REMARKS

Reconsideration of this application is respectfully requested in view of the following remarks.

I. Claim Status

Claims 1-19, and 21-24 are pending.

Claim 1 has been amended to more clearly point out that prolactin resetting therapy involves conforming the daily prolactin profile of a tumor-bearing mammal such that the peak and trough of the daily prolactin profile of the tumor-bearing mammal occurs at or about the same time as the peak and trough of the daily prolactin profile of a healthy mammal of the same species and sex. Support for the claim as amended can be found throughout the specification, e.g., Figure 1; p. 13. lines 16-27; p. 14, lines 16-22; and p. 15, lines 3-5.

II. Rejections for Obviousness-Type Double Patenting and Under 35 U.S.C. §103 over U.S. Patent No. 5,792,748, Werning, and Cincotta

Claims 1-3, 6, 10, 15, 20, 21 and 22 have been rejected under the judicially created doctrine of obviousness-type double patenting, as allegedly obvious over claims 3, 8, 13 and 19 of the '748 patent in view of Werning et al., *Arch. Ontolaryngol. Head Neck Surg.* 121:783-789 (995) ("Werning") and Cincotta et al., *Cancer Res.* 54:1249-1258 (1994) ("Cincotta"), as evidenced by Molitch, *Endocrinol. Metab. Clin. North Am.* 21:(4) (abstract) (1992) ("Molitch").

Claims 1-19, and 21-24 have been rejected as allegedly obvious over the '748 patent in view of Werning and Cincotta as evidenced by Molitch.

Applicants note that obviousness-type double patenting rejections may frequently be addressed by filing a terminal disclaimer. This procedure is only available, however, if the pending application and the patent used to make the rejection are owned by (i.e., assigned to) the same parties. A terminal disclaimer cannot be used here because the application is assigned to The

General Hospital Corporation and the President and Fellows of Harvard College, whereas the '748 patent is assigned to The General Hospital Corporation and the Board of Supervisors of Louisiana State University and Agricultural and Mechanical College (LSU), and the '914 patent is assigned to LSU and VeroScience, LLC. The arguments set forth below apply equally to the obviousness-type double patenting rejection and the obviousness rejection. Accordingly, these rejections are traversed together, on the grounds that there is no suggestion to combine the '748 patent with Werning and Cincotta to arrive at a method of treating tumors by combining neuroendocrine resetting therapy (NRT) with photodynamic therapy (PDT).

The claims are drawn to treating tumors in a mammal with PDT in combination with NRT using a prolactin enhancer, i.e., administering the prolactin enhancer at appropriate time intervals of day such that the daily plasma prolactin profile of a tumor bearing mammal conforms to or approaches the normal daily plasma prolactin profile for healthy members of the same species and sex of the mammal. The prior art cited by the Examiner discloses treating tumors separately with PDT or NRT, but not in combination. The Examiner's position is that the cited references teach that the combination of photodynamic therapy with administration of a prolactin enhancer results in the increased regression of tumors versus photodynamic therapy alone. Specifically, the Examiner contends that the '748 patent discloses and claims a method for inhibiting neoplasm growth in humans by comparing the prolactin profile of the afflicted human to a standard prolactin profile for healthy humans of the same sex and adjusting the prolactin profile of the afflicted human via administration of a prolactin enhancer, such as melatonin in a certain amount and at certain times. The Examiner also asserts that Werning discloses that the combination of photodynamic therapy with metoclopramide increases the percentage of tumor regression versus photodynamic therapy alone. The Examiner cites Molitch for evidence that metoclopramide is a prolactin enhancer. According to the Examiner, it would have been obvious to one of ordinary skill in the art to optimize the invention claimed in the '748 patent so as to include PDT.

The Examiner's stated suggestion fails, however, because the effect observed in Werning is completely unrelated to metoclopramide's action on prolactin and, more particularly, is completely unrelated to resetting the prolactin rhythm of a tumor bearing mammal. The Examiner asserts that applicants' position that the effect observed in Werning is unrelated to resetting the prolactin rhythm of a tumor-bearing mammal is "mere speculation." With all due respect, the Examiner is incorrect. Prolactin resetting therapy ("PRT") and PDT are two different types of therapy, as evidenced by the instant specification and the claimed invention, which combines PRT and PDT. The Werning reference relates to only one therapy, PDT, more specifically enhancement of PDT. This is evidenced throughout the Werning, indeed starting with its title, which recites that metoclopramide "enhances the effect of photodynamic therapy ...." In addition, Werning and his co-authors state very clearly that "our research efforts are aimed toward improving the clinical response to PDT" (Werning, p. 788, top of column 2), and that the experimental goal of Werning and his co-authors was to "assess the potentiating effects of metoclopramide." (Werning, p. 785, column 1, first full paragraph). Furthermore, the authors note that the metoclopramide in Werning is **not** used for its effects on prolactin profile, but is instead "used to enhance the effects of ionizing radiation and chemotherapy" (*see, e.g.*, p.785, column 1, second full paragraph). Thus, all discussion in Werning is restricted to metoclopramide and the effects directly attributable to metoclopramide. On the other hand, there is simply no disclosure in Werning that the effect obtained by combining metoclopramide administration and PDT is related in any way to plasma prolactin levels. In fact, prolactin is not mentioned even once in Werning. Hence, Werning suggests that metoclopramide can sensitize tumor cells to chemotherapy and radiation therapy, that metoclopramide has the ability to damage DNA directly and inhibit the repair of DNA damage caused by other agents and that metoclopramide has been reported to increase the distribution of blood flow to tumors. (*See* Werning, page 787, bottom of column 1 – p. 788, column 2). Werning fails to make any suggestion, however, that these effects are mediated through plasma prolactin levels. In addition, Werner fails completely to teach or suggest that administration of metoclopramide must occur at specific times over a 24-hour period in order to adjust the daily plasma prolactin so that the peak and trough of the daily prolactin profile of the tumor-bearing mammal occurs at or about the same time as the peak and trough of the daily prolactin profile of a

healthy mammal of the same species and sex, as required in the claims as amended. In fact, if one of ordinary skill in the art modified the Werning teaching that metoclopramide should be administered at 1 hour before and 24 and 48 hours after PDT, and instead administered metoclopramide within the peak prolactin period of said healthy mammal of the same species and sex as said tumor bearing mammal, as required by the claims, this would serve to render the Werning method inoperable for its intended use, i.e., **enhancement** of PDT. It is well established law that when combining prior art references to modify the claimed invention would render the prior art inoperable for its intended use, the references cannot be properly combined. *In re Ratti*, 270 F.2d 810 (CCPA 1959); MPEP 2143.01. Furthermore, Werning teaches that there is a direct dose response correlation between the metoclopramide dose and tumor ablation. Doses of 16, 32, and 48 mg/kg, respectively, showed the greatest efficacy in treating tumors when used to enhance PDT. Accordingly, Werning teaches that the metoclopramide dose should be maximized to effect enhancement of PDT for tumor treatment. However, if one of ordinary skill in the art attempted to employ the teachings of Werning (administration of high doses (16, 32, and 48 mg/kg) of metoclopramide at 1 hour before and 24 and 48 hours after PDT) to reset prolactin levels, such an attempt would fail – such a method of increasing metoclopramide doses would not serve to reset prolactin levels, but would instead result in uniformly high prolactin levels. In summary, then, Werning teaches away from the claimed invention in two respects: first, the metoclopramide in Werning is **not** used for its effects on prolactin profile, but is instead used to enhance the effects of ionizing radiation and chemotherapy; and second, the method of increasing metoclopramide doses, as taught in Werning, would not serve to reset prolactin levels, but would instead result in uniformly high prolactin levels.

Accordingly, Werning fails to provide any suggestion that metoclopramide be used to adjust the daily plasma prolactin profile of a tumor bearing mammal, in combination with PDT.

Nor does Molitch's disclosure that metoclopramide is a prolactin enhancer provide a suggestion to combine Cincotta with Werning to arrive at the instant claims, in view of Werning's teaching that the prolactin enhancing activity of metoclopramide is not related to the observed enhancement of PDT. In fact, Werning's incompatibility with the '748 patent is supported by

Molitch. Hence, Molitch states that, "Pathologic increases of PRL [prolactin] owing to hypothalamic dysregulation occur with a variety of medications, including…metoclopramide." (Molitch, lines 12-14). Accordingly, Molitch does not provide evidence that metoclopramide, as administered in Werning, is a prolactin enhancer that may be used in combination with '748 patent to arrive at the instant claims. To the contrary, Molitch teaches explicitly that metoclopramide **cannot** be used to reset the daily plasma prolactin profile of a tumor bearing mammal to approach the profile of a normal mammal. Hence, Molitch and Werning teach away from each of the '748 patent and the instant claims. Thus, one of ordinary skill in the art could not combine Werning, as evidenced by Molitch, with the '748 patent to arrive at the instant claims.

For at least the reasons set forth above, none of the prior art cited by the Examiner suggests any motivation or benefit to treating tumors by the combination of adjusting the plasma prolactin profile of a tumor bearing mammal to approach or conform to the profile of a healthy mammal with PDT. For at least this reason, the instant rejections should be withdrawn.

Unexpected results are obtained with the combination of prolactin resetting therapy and PDT, compared to either therapy alone

Additionally, the claims are not obvious over the combination of the teachings of the cited references because unexpected results are obtained with the combination of neuroendocrine resetting therapy and PDT, compared to either therapy alone. Examples 1 and 2 and Figure 5 of the application demonstrate the synergistic effects when PDT is combined with NRT using a prolactin enhancer, as called for in the claims. There is no suggestion in the prior art that such synergistic effects could be achieved.

Thus, Example 1, set forth on page 28 of the instant specification, describes an experiment designed to measure the effect of control (C), prolactin (PRL; 20 mcg/mouse at 10 h after light onset at 7 days after tumor inoculation, continuing for 14 days), PDT (D+L; EtNBS photosensitizer; power density of 100J/cm^2 and a total energy of 100J/ cm^2) and prolactin plus PDT (D+L+PRL) treatments on tumors in EMT-6 tumor bearing mice. The results of the experiment that are shown in Figure 5 demonstrate the unexpected synergistic effect of the combined treatment.

As shown in Figure 5, the average tumor volume in EMT-6 tumor bearing animals treated with prolactin alone was found to be 56% of the average tumor volume of control animals (i.e., prolactin treatment reduced average tumor volume by 44%). The average tumor volume in EMT-6 tumor bearing animals treated with PDT alone was 43% of the average tumor volume for control animals (i.e., PDT reduced average tumor volume by 57%). Based on these results, therefore, the average tumor volume in EMT-6 tumor bearing animals treated with both prolactin and PDT, obtained by multiplying the results of each individual treatment (i.e., 0.56 X 0.43), is predicted to be 24% of the average tumor volume of control animals (i.e., 76% reduction in the average tumor volume compared to control cells).

The results given in Figure 5 demonstrate, however, that the combined treatment with prolactin and PDT is more effective than the results predicted from the combination of each treatment alone. Hence, the combined treatment actually reduced average tumor volume by 92.4%, compared to control animals, and compared to the predicted value of 76% for the combined treatment. Stated differently, the results showed that the average tumor volume of animals that received the combined treatment was only 7.6% the average tumor volume of control animals. This value is over 3-fold lower than the value of 24% predicted for the combined treatment, based on the results of the individual treatments. Hence, the combined treatment with PDT and prolactin lead to an unexpectedly greater reduction in tumor volume than that predicted from the results obtained with each treatment alone. The results of Example 1 are therefore objective evidence of the remarkable results achieved by the combined treatment over either treatment alone.

Further experimental evidence of the synergy obtained in treating tumors with a prolactin enhancer and PDT is set forth in Example 2 (see specification at pages 28-29). Example 2 reports that, when PDT with the benzophenothiazine photosensitizer EtNBS is used alone, at a power density of 50 mW/ cm^2 and a total energy of 180 J, tumor "cure" (tumor-free for at least 90 days) of 4-8 mm diameter tumors can be achieved in 70-100% of the cases, and is largely dependent upon the tumor size at the time of PDT. In contrast, if intraperitoneal prolactin is administered (20

mcg/mouse/day at 10 h after light onset, starting from day of tumor cell inoculation) in conjunction with PDT, then the cure rate is 100%. Furthermore, the time course of tumor eradication is significantly faster with the combined treatment versus PDT alone. Hence, tumors remained noticeable 48-72 h following PDT treatment alone, taking 14 days to regress completely, with eschar formation at 24-48 hours. In contrast, when timed administration of prolactin was combined with PDT, 100% of the treated animals exhibited eschar formation and complete tumor eradication within 24 h of PDT. Hence, in Example 2, the combination of neuroendocrine resetting therapy and PDT lead to more rapid tumor eradication and a higher tumor eradication rate (i.e., 100%), compared to PDT alone.

Moreover, the timing of prolactin administration is essential in order to obtain the synergistic effect of PDT and prolactin treatment. The specification makes it clear that prolactin should be administered during the time of the plasma prolactin peak in a healthy mammal of the same sex.

III. Rejection for Obviousness-Type Double Patenting over the '914 Patent in view of Lin and Cincotta

Claims 1-4, 10, 15, 20 and 21 have been rejected for obviousness-type double patenting over claims 12, 13, 28 and 30 of Cincotta et al., U.S. Patent No. 6,071,914 ("the '914 patent"), in view of Lin, *Cancer Cells*, 1991, 3:4.

For the reasons identical to those set forth above in Section IV the claims are not obvious over the combination of the teachings of the '914 patent and Cincotta, because unexpected results are obtained with the combination of NRT and PDT, compared to either therapy alone.

IV. Conclusion

For the reasons set forth above, applicants respectfully request withdrawal of the nonstatutory double patenting rejections and the rejection for obviousness under 35 U.S.C. § 103.

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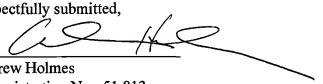
Respectfully submitted,

By 

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